

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP2004/012469

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 G01N33/574 C12Q1/68

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 G01N C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BIOSIS, WPI Data, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|----------|--|-----------------------|
| Y | <p>VIRTANEVA K ET AL: "EXPRESSION PROFILING REVEALS FUNDAMENTAL BIOLOGICAL DIFFERENCES IN ACUTE MYELOID LEUKEMIA WITH ISOLATED TRISOMY 8 AND NORMAL CYTOGENETICS" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, NATIONAL ACADEMY OF SCIENCE, WASHINGTON, US, vol. 98, no. 3, 30 January 2001 (2001-01-30), pages 1124-1129, XP002952627 ISSN: 0027-8424 cited in the application the whole document</p> <p>-----</p> <p style="text-align: center;">-/-</p> | 1-27 |

 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

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| Date of the actual completion of the international search | Date of mailing of the international search report |
| 2 March 2005 | 13.07.2005 |
| Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016 | Authorized officer Thumb, W |

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|---|-----------------------|
| Y | <p>QIAN ZHIJIAN ET AL: "Expression profiling of CD34+ hematopoietic stem/ progenitor cells reveals distinct subtypes of therapy-related acute myeloid leukemia" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, NATIONAL ACADEMY OF SCIENCE. WASHINGTON, US, vol. 99, no. 23, 12 November 2002 (2002-11-12), pages 14925-14930, XP002261373 ISSN: 0027-8424 abstract page 14927, column 2</p> <p>-----</p> <p>WO 03/039443 A (DEUTSCHES KREBSFORSCH ; HAFLERLACH TORSTEN (DE); EILS ROLAND (DE); K) 15 May 2003 (2003-05-15) the whole document in particular Example 7, page 125</p> <p>-----</p> <p>DATABASE BIOSIS [Online] BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; 16 November 2001 (2001-11-16), CHEN GUIBIN ET AL: "Distinct gene expression profile in CD34 cells from patients with specific karyotypic defects in myelodysplasia" XP002273025 Database accession no. PREV200200250081 abstract & BLOOD, vol. 98, no. 11 Part 1, 16 November 2001 (2001-11-16), pages 728a-729a, 43rd Annual Meeting of the American Society of Hematology, Part 1; Orlando, Florida, USA; December 07-11, 2001 ISSN: 0006-4971</p> <p>-----</p> <p>DATABASE BIOSIS [Online] BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; 16 November 2002 (2002-11-16), VEY NORBERT ET AL: "Gene Expression Profiling of Acute Myeloid Leukemias with Normal Karyotype." XP002273026 Database accession no. PREV200300357083 abstract</p> | 1-27 |
| Y | | 1-27 |
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|----------|--|-----------------------|
| Y | <p>& BLOOD, vol. 100, no. 11, 16 November 2002 (2002-11-16), page Abstract No. 2949, 44th Annual Meeting of the American Society of Hematology;Philadelphia, PA, USA; December 06-10, 2002 ISSN: 0006-4971</p> <p>-----</p> <p>DATABASE BIOSIS [Online] BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; 16 November 2002 (2002-11-16), QIAN ZHIJIAN ET AL: "Expression Profiling of CD34+ Hematopoietic Progenitors Reveals Distinct Subtypes of Therapy-Related Acute Myeloid Leukemia." XP002273027 Database accession no. PREV200300335806 abstract & BLOOD, vol. 100, no. 11, 16 November 2002 (2002-11-16), page Abstract No. 1206, 44th Annual Meeting of the American Society of Hematology;Philadelphia, PA, USA; December 06-10, 2002 ISSN: 0006-4971</p> <p>-----</p> | 1-27 |
| Y | <p>DATABASE BIOSIS [Online] BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; 16 November 2002 (2002-11-16), RITTER MARKUS ET AL: "Differentially Regulated Signaling Pathways in AML with Monosomy 7 and 7q-." XP002273028 Database accession no. PREV200300367793 abstract & BLOOD, vol. 100, no. 11, 16 November 2002 (2002-11-16), page Abstract No. 4309, 44th Annual Meeting of the American Society of Hematology;Philadelphia, PA, USA; December 06-10, 2002 ISSN: 0006-4971</p> <p>-----</p> | 1-27 |
| Y | <p>EP 1 043 676 A (WHITEHEAD BIOMEDICAL INST) 11 October 2000 (2000-10-11) the whole document</p> <p>-----</p> | 1-27 |
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|---|-----------------------|
| Y | <p>GOLUB T R ET AL: "Molecular classification of cancer: Class discovery and class prediction by gene expression monitoring" SCIENCE, AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE,, US, vol. 286, no. 5439, 15 October 1999 (1999-10-15), pages 531-537, XP002207658 ISSN: 0036-8075 cited in the application the whole document</p> <p>-----</p> | 1-27 |
| Y | <p>DATABASE BIOSIS [Online] BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; 16 November 2002 (2002-11-16), KOHLMANN ALEXANDER ET AL: "A Simplified and Partially Automated Target Preparation Method for Gene Expression Profiling." XP002269495 Database accession no. PREV200300367771 abstract & BLOOD, vol. 100, no. 11, 16 November 2002 (2002-11-16), page Abstract No. 4287, 44th Annual Meeting of the American Society of Hematology;Philadelphia, PA, USA; December 06-10, 2002 ISSN: 0006-4971</p> <p>-----</p> | 1-27 |
| Y | <p>HAFERLACH T ET AL: "The Diagnosis of 14 Specific Subtypes of Leukemia Is Possible Based on Gene Expression Profiles: A Study on 263 Patients with AML, ALL, CML, or CLL" BLOOD, W.B.SAUNDERS COMPAGNY, ORLANDO, FL, US, vol. 100, no. 11, 16 November 2002 (2002-11-16), page 139A, XP002263227 ISSN: 0006-4971 the whole document</p> <p>-----</p> | 1-27 |
| Y | <p>KOHLMANN A ET AL: "MOLECULAR CHARACTERIZATION OF ACUTE LEUKEMIAS BY USE OF MICROARRAY TECHNOLOGY" GENES, CHROMOSOMES & CANCER, XX, XX, vol. 37, no. 4, August 2003 (2003-08), pages 396-405, XP008025253 the whole document</p> <p>-----</p> <p>-/-</p> | 1-27 |

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International Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|---|-----------------------|
| Y | DUGAS MARTIN ET AL: "Impact of integrating clinical and genetic information." IN SILICO BIOLOGY, vol. 2, no. 3, 2002, pages 383-391, XP001179418 ISSN: 1386-6338 (ISSN print) the whole document ----- | 1-27 |
| Y | DUGAS M ET AL: "A comprehensive leukemia database: integration of cytogenetics, molecular genetics and microarray data with clinical information, cytomorphology and immunophenotyping" LEUKEMIA, MACMILLAN PRESS LTD, US, vol. 15, no. 12, December 2001 (2001-12), pages 1805-1810, XP002263731 ISSN: 0887-6924 the whole document ----- | 1-27 |
| A | ALIZADEH A ET AL: "THE LYMPHOCHIP: A SPECIALIZED CDNA MICROARRAY FOR THE GENOMIC-SCALE ANALYSIS OF GENE EXPRESSION IN NORMAL AND MALIGNANT LYMPHOCYTES" COLD SPRING HARBOR SYMPOSIA ON QUANTITATIVE BIOLOGY, BIOLOGICAL LABORATORY, COLD SPRING HARBOR, NY, US, vol. 64, no. 1, 1999, pages 71-78, XP001099007 ISSN: 0091-7451 the whole document ----- | 1-27 |
| A | WO 03/083140 A (WONG LIMSOON ; YEOH ENG-JUH (SG); DOWNING JAMES R (US); WILKINS DAW) 9 October 2003 (2003-10-09) table 63 ----- | 1-27 |

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Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:

Article 52 (2)(d) EPC - Presentation of information

The claims were only searched with regards to the underlying method of generating a reference data base for distinguishing AML subtypes with

2. Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-27 (partially)

Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.1

Article 52 (2)(d) EPC - Presentation of information

The claims were only searched with regards to the underlying method of generating a reference data base for distinguishing AML subtypes with different gene dosages.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-27 (partially)

A method for distinguishing AML+11 from AML TRI+8, AML TRI+13, AML-M07, AML-DEL5q, and/or AML-DEL9, the method comprising determining the expression level of the marker ITGAE (CD103). Use of said marker for the manufacture of a diagnostic. A diagnostic kit containing said marker and an apparatus comprising a reference data bank, wherein the reference data bank is obtainable by determining the expression level of ITGAE.

2. claims: 1-27 (all partially)

Inventions 2-1400

Methods for distinguishing AML subtypes with different gene dosages selected from AML TRI+8, AML TRI+11, AML TRI+13, AML-M07, AML-DEL5q, and/or AML-DEL9q, and methods for distinguishing specific subtypes against all other AML subtypes and against each other, the methods comprising determining individually the expression level of the markers listed in tables 1.1, positions 2-50, tables 1.2-1.7 and in table 2. Use of said markers for the manufacture of diagnostics. Diagnostic kits containing said markers and apparatus comprising a reference data bank, wherein the reference data bank is obtainable by determining the expression levels of said markers.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
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| Patent document cited in search report | Publication date | Patent family member(s) | | Publication date |
|--|------------------|-------------------------|---------------|------------------|
| WO 03039443 | A 15-05-2003 | EP 1308522 | A1 07-05-2003 | |
| | | WO 03039443 | A2 15-05-2003 | |
| | | EP 1470247 | A2 27-10-2004 | |
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| | | EP 1043676 | A2 11-10-2000 | |
| | | JP 2001017171 | A 23-01-2001 | |
| | | US 2003017481 | A1 23-01-2003 | |
| | | US 6647341 | B1 11-11-2003 | |
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| | | WO 03083140 | A2 09-10-2003 | |
| | | US 2004018513 | A1 29-01-2004 | |